AR201-13781

Eastman Chemical Company
P.O. Box 511
Kingsport, Tennessee 37662

EASTMAN

May 22, 2002

Ms. Christine Todd Whitman, Administrator
U.S. EPA
P.O. Box 1473
Merrifield, VA 22116

Attn: Chemical Right-to-Know Program

RE: HPV Chemical Challenge Program, AR-201

Dear Ms. Whitman:

This letter is submitted by Eastman Chemical Company and The Dow Chemical Company in response to comments received from the Environmental Protection Agency ("EPA") dated April 8, 2002 following EPA's review of the test plan and robust summaries for 3-ethoxypropionic acid ethyl ester (CAS No.: 763-69-9). We thank the EPA for its review and welcome the recognition of its completeness and fulfillment of our obligation to this chemical in the HPV program.

Below are the EPA's comments to various sections of the test plan and robust summaries and how we have addressed those concerns:

Test Plan

1. Chemistry (melting point, boiling point, vapor pressure, water solubility, and partition coefficient).

   EPA agrees that the submitters' approach to these endpoints, except for vapor pressure and water solubility, is acceptable for the purposes of the HPV Challenge Program. The submitters need to provide measured values for vapor pressure and water solubility. The use of estimated values introduces uncertainties that then become magnified in modeling applications.

To address this comment we have modified all the robust summaries for the physical chemistry endpoints through the use of a more recent version of EPIWIN (v3.10 vs. v1.2) from which these endpoints were originally estimated. We disagree with the comment that we need to obtain measured values for vapor pressure and water solubility. The Agency has previously indicated in their guidance document "*The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program*" estimations using an appropriate model will be accepted for all physicochemical endpoints. The models noted to be acceptable within that guidance document are those found within EPIWIN suite.

2. Environmental Fate (Photodegradation, Stability in Water, Biodegradation, Fugacity).

   EPA agrees that the submitters' approach to these endpoints, except for stability in water, is acceptable for the purposes of the HPV Challenge Program.

   Stability in Water.
   The submitters state that 3-ethoxypropionic acid ethyl ester is not readily hydrolyzed, with estimated half-lives of 102.8 days and 2.8 years at pH values of 8 and 7, respectively, using the HYDROWIN v. 1.67 estimation model. EPA prefers that the submitters provide measured data for stability in water. Having accurate measured water stability data is important because it provides information on the persistence of a chemical in the aquatic environment. Furthermore, according to OECD Guideline 111, a compound that has a half-life of greater than one year at 25C is considered hydrolytically stable and further testing is not required. As the half-life of this compound at pH 8 is less than one year, the submitters need to provide measured hydrolysis data.

While the Agency prefers to have measured data, we believe the use of the HYDROWIN v. 1.67 estimation model should be deemed as acceptable to meet this endpoint. It is noted that this program was developed to predict the hydrolysis rate constants for specific types of compounds, including esters, which is the chemical class that our compound belongs to.

3. Health Effects (acute toxicity, repeat dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

   EPA agrees that data are adequate for purposes of the HPV Challenge Program. However, the robust summary for developmental toxicity needs to be modified. (See "Specific Comments on Robust Summaries" below.)

This comment is addressed below in the section "Specific Comments on the Robust Summaries."

4. Ecotoxicity (fish, invertebrate and algal toxicity).

   EPA agrees that data are adequate for fish and daphnia for purposes of the HPV Challenge Program. However, EPA questions the validity of the algal data. It was reported in the robust summary that there was no effect on algal growth at a single concentration in a limit test. However, the effective concentration for growth inhibition is predicted to be significantly lower than the concentration tested, based on structure-activity relationships (ECOSAR). Also, the basis for selecting the test concentration was not reported. EPA requests a copy of the full report from this study to determine if additional testing is needed for this endpoint.

We too agree that the data submitted for the fish and daphnia are adequate to fulfill these endpoints. These data are from well-documented studies that followed established guidelines and were conducted under GLP assurances. The validity of the information within them is readily transparent from the information contained in the robust summaries. The concern the Agency has over the validity of the algal study is puzzling. This study was also a robust study that followed established guidelines and was conducted under GLP assurances. The fact that the modeling data predicted a lower level of concern was the basis for obtaining the actual data. The concentration selected (100 mg/L) is the lowest level required in a limit study such that if no affects are seen at this level than there is no need to pursue lower concentrations. As all study information needed to determine its validity is present within the robust summary, we do not believe there is a need to send a copy of this study into the Agency.

Specific Comments on the Robust Summaries

5. Health Effects

Acute Oral Toxicity. For the cited supplementary study, the submitters need to add the date, report title, and report number.

Acute, Repeated Dose, and Reproductive Toxicity (Inhalation). The submitters need to indicate the method by which the test atmosphere was generated (e.g., as aerosol, vapor, etc.).

The robust summaries have been modified to include the requested information.

Genetic Toxicity - Chromosomal Aberration. The submitters need to add the study title, the concentration levels, the number of replicates/concentration, and the number of metaphases per concentration that were examined.

The robust summary has been modified to include all the requested information. However, as no evidence of genotoxicity was noted at the maximum concentration required by the guideline (>10 mM), we have not added all the lower concentration levels tested. These varied throughout the assay depending on the endpoint assessed (e.g., cytotoxicity, initial verse confirmatory assay).

Developmental Toxicity (Inhalation). For both the rat and rabbit studies, the submitters need to state the method by which the test atmosphere was generated (e.g., aerosol, vapor, etc.). For the rat study, EPA disagrees with the selection of the NOAEL of 1000 ppm for developmental toxicity because increased incidences of soft tissue alterations and skeletal variations were seen in litters at this dose level with slightly greater than minimal maternal toxicity.

The robust summaries have been modified to include the physical form (vapor) in which the animals were exposed to the test article. The summaries have also been modified to clearly distinguish that the effects noted in the fetuses at 1000 ppm were indicative of fetotoxicity and do not represent evidence for teratogenicity. Accordingly, we have stated a specific NOEL for fetotoxicity (500 ppm) and for teratogenicity (1,000 ppm) within the new summary.

Enclosed with this letter is a computer diskette containing the test plan and modified robust summaries in Adobe Acrobat (.pdf) format. The HPV registration number for Eastman Chemical is

Sincerely,

James A. Deyo, D.V.M., Ph.D., D.A.B.T.
Technical Associate

Enclosure

cc: Dr. Bill Snellings, Dow Chemical Company